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ORIGINAL ARTICLE

Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation

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Summary

The aim of this study was to determine the efficacy, safety, and immunosuppressant adherence in 125 stable liver transplant (LT) patients converted from twice-daily tacrolimus (TAC BID) to once-daily TAC (TAC OD). Tacrolimus trough levels, laboratory parameters, metabolic disorders, selected patient reported outcomes, and adverse events were assessed. Mean TAC trough level concentration was 6.1 ± 2.3 ng/ml at study entry, decreased to 5.5 ± 2.1 ng/ml ($P = 0.016$) and 5.5 ± 2.2 ng/ml ($P = 0.019$) after 1 and 2 weeks, respectively, and tended to equal the baseline value during further follow-up. At week 1, TAC concentrations were lower in 62.4% of patients and higher in 36.0% when compared with baseline. Renal and cardiovascular risk factors remained stable and no rejection episodes occurred over 12 months. Adverse events were consistent with the safety profile known from previous studies with TAC BID. Nonadherence measured by the "Basel Assessment of Adherence Scale to Immunosuppressives" was evident in 66.4% at study entry and decreased to 30.9% postconversion ($P < 0.0001$). Prevalence of nonadherence at baseline was significantly higher in patients converted >2 years after LT and in those ≤60 years of age. Conversion to TAC OD is safe, enhances immunosuppressant adherence and should be accompanied by a close TAC level monitoring during the initial period.

Introduction

Life-long intake and complexity of immunosuppressive medication make patients prone to nonadherent behavior which contributes to rejection and graft loss [1]. Drug adherence declines over the course of time in patients after organ transplantation and depends on the type of medication, the number of drugs to be taken and the number of daily doses [2]. A study in kidney transplant patients demonstrated that once-daily (OD) dosing resulted in improved adherence when compared with twice-daily (BID) dosing [3]. Similarly, a review of 76 studies using electronic monitoring device to assess medication adherence showed that the prescribed number of doses per day was inversely related to adherence [4].

The introduction of OD tacrolimus (TAC OD) extended-release (XL) formulation, administered in the morning, may be associated with better treatment

adherence and quality of life. A previously published phase 3 randomized study in *de novo* liver transplant (LT) patients compared TAC OD with TAC BID, both combined with corticosteroids [5]. One year results demonstrated that the new TAC formulation-based regimen had a similar efficacy and safety profile when compared with TAC BID. A pharmacokinetic conversion study in stable LT recipients reported equivalent, but on average 11% lower AUC_{0-24} after a milligram (mg)-for-mg dose conversion [6]. In a *de novo* study of LT patients, systemic exposure (AUC_{0-24}) on day 1 was approximately 42% lower for TAC OD than for TAC BID at equivalent doses, whereas values at steady state (day 14 and week 6) were similar for both formulations [7]. To our knowledge, no prospective studies have been published in full addressing selected patient reported outcomes (PROs) (e.g., adherence to immunosuppressive medication or patients' treatment preferences) in stable LT patients who have been switched from a conventional TAC-based regimen to the new TAC formulation. We therefore addressed this issue over a 1-year study period. Moreover, we assessed metabolic and cardiovascular risk factors and potential adverse events postconversion.

Patients and methods

Design and sample

This study was designed as a prospective, single center, observational, noninterventional study with 8 time points: preconversion (baseline), weeks 1 and 2, and months 1, 3, 6, 9, and 12 after conversion (Fig. 1).

Adult LT patients were eligible for the study if they (i) had received a primary deceased or living related LT >6 months prior to study entry and (ii) were willing to comply with the study protocol. Exclusion criteria were (i) the presence of systemic infection requiring therapy, (ii) pregnant and nursing women, (iii) signs of decompensated liver disease, (iv) severe or recurrent gastrointestinal complaints, or (v) an episode of chronic or acute graft rejection within 12 months of study entry.

As this was an observational study, the assignment of patients to the new TAC formulation fell within current practice in accordance with the terms of the marketing authorization and the prescription of the medicine was clearly separate from the decision to include a given patient in the study. No diagnostic or monitoring procedures other than those required in the course of current clinical practice were applied to the patients. The study was approved by the Institutional Review Board of the University of Duisburg-Essen (IRB 07-3557). All patients gave written informed consent in accordance with the Declaration of Helsinki 2000 and the Declaration of Istanbul 2008.

Therapeutic protocol and adjunct immunosuppressants

The switch from a TAC BID (Prograf®; Astellas Phrama US, Inc., Deerfileld, IL, USA) to a TAC OD (Advagraf®; Astellas Phrama US, Inc., Deerfileld, IL, USA) regimen was based on a 1:1 mg proportion. We instructed our patients to administer TAC BID or the new TAC XL

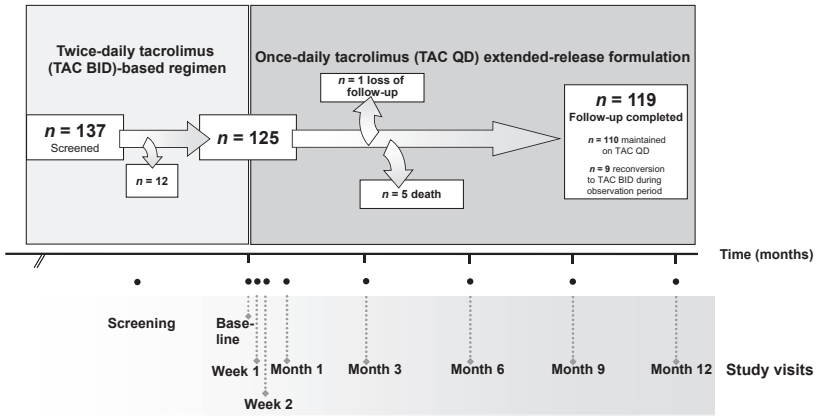

Figure 1 Study design and flow chart with disposition of patients. A total of 137 patients were screened; 125 patients successfully completed the screening phase and 12 were withdrawn for reasons of severe decompensated liver disease [fibrosing cholestatic hepatitis C (n = 1), recurrent alcohol-related graft failure (n = 1), severe diarrhea (n = 3), chronic rejection (n = 3), acute cellular rejection (n = 1), inability (n = 1) and unwillingness to comply to the study protocol (n = 1)]. During the study, one patient was lost to follow-up after 21 days and five patients died because of sepsis (n = 3), recurrent neuroendocrine tumor (n = 1) and fibrosing cholestatic hepatitis C (n = 1) after 233, 327, 328, 23, and 79 days, respectively. A total of 119 patients completed 12 months of follow-up; of those, n = 110 had continuous administration of TAC OD formulation throughout the study; whereas nine patients were switched back to TAC BID because of adverse events.

formulation according to the product information provided by the company.

At baseline and during follow-up, TAC doses were adjusted to maintain target trough levels of 4–8 ng/ml. TAC levels were measured in our central laboratory at baseline, weeks 1 and 2, months 1, 3, 6, 9, and 12 using the affinity column-mediated immunoassay (Dimension RxL Max; Dade Behring, Eschborn, Germany).

A total of 55 patients were receiving adjunctive immunosuppressive medications prior to study entry. Sirolimus (SRL) was adjusted to maintain target trough levels of 5–7 ng/ml. Concomitant prednisone dose was low, ranging from 2.5 mg to 7.5 mg/day.

Primary and secondary objectives

The primary objective of the study was to determine the event rate of biopsy-proven acute rejection within 12 months postconversion. Secondary objectives included patient and allograft survival, renal function [measured by serum creatinine and calculated glomerular filtration rate (cGFR)], liver enzymes, adverse events and PROs (adherence to immunosuppressive regimen and patients' preference with TAC OD versus TAC BID) at 1 year.

Clinical and biochemical parameters

Patient and graft survival and the time to and the event rate of biopsy-proven acute rejection episodes were assessed throughout the study. A liver biopsy was performed if clinical signs and/or laboratory parameters were suspicious of the occurrence of a rejection episode. Histological evaluation of the biopsy was performed according to the Banff criteria [8]. Graft loss was defined as retransplantation or death.

Blood pressure was recorded at each visit. Arterial hypertension was diagnosed when systolic blood pressure was ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or in case of current antihypertensive treatment [9]. Diabetes was defined according to the American Diabetes Association Diagnostic Criteria [10]. Hypercholesterolemia was diagnosed in patients with fasting total cholesterol level of >200 mg/dl or the need for cholesterol-lowering agents; hypertriglyceridemia was defined as fasting total triglyceride level of >200 mg/dl or the need for triglyceride-lowering agents.

Safety was determined at each visit based on physical examination, vital sign measurements, adverse events, and results of laboratory tests. Patients had regular monitoring of laboratory values at months 0, 1, 6, 9, and 12. HbA1c was determined at months 0, 1, 6, and 12; cGFR was calculated based on the abbreviated modification of diet in renal disease (MDRD) equation [11].

Patient reported outcomes

Self-reported adherence with immunosuppressive therapy was assessed at baseline and at month 12 using the "Basel Assessment of Adherence Scale to Immunosuppressives" (BAASIS). This instrument consists of a four-item validated questionnaire and a Visual Analog Scale (VAS) [12,13]. The BAASIS is administered as a patient interview, and the recall period comprises the last 4 weeks.

The second part of the BAASIS is a 100-point VAS scale. Patients score their medication adherence during the past 4 weeks from 0 (immunosuppressive medication never taken as prescribed) to 100 (immunosuppressive medication always taken as prescribed) [14]. Medication adherence is assessed as a continuous variable by the VAS with no defined cut-off for nonadherence.

Patients' preference with the treatment regimen was also assessed by a self-report at the end of the observation period. More specifically, patients were asked whether they preferred to remain on TAC OD or return to TAC BID regimen. Patients who decided to remain on TAC OD formulation after study completion were asked at month 12 to specify the reason for drug continuation.

We further investigated the possible implications of therapeutic complexity, reflected by the number of prescribed drugs and the dosing frequency, on drug adherence. For this purpose, we reviewed the patients' records and listed all of the concomitant medication for those patients ($n = 110$) in whom adherence was measurable at baseline and follow-up, and who were maintained on TAC OD throughout the study. We also investigated whether there was a correlation between age and adherence and a difference in the adherence of patients converted during a shorter (≤2 years) versus a longer time period (>2 years) after LT.

Statistical analysis

Continuous data were expressed as mean ± SD (unless otherwise indicated). Friedman test was used to compare continuous values at distinct time points for global comparison. An overall $\alpha = 0.05$ was chosen to indicate statistical significance. A Wilcoxon Signed Rank test was carried out to compare continuous values at two distinct time points (visits) and to compare the follow-up data with the baseline data. Categorical data were described as frequencies of the subjects with a specific characteristic. Chi-square test was used to compare categorical data and the McNemar test was used to compare paired categorical variables. The Pearson's rank correlation coefficient was used to measure the degree of association between two quantitative variables. Two-tailed P values <0.05 were

considered statistically significant. Statistical analyses were performed using SPSS software 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

Between September 2008 and June 2009, 137 LT recipients with TAC BID-based immunosuppression were screened for eligibility criteria (Fig. 1). Of these, 125 LT recipients were switched to TAC OD, whereas 12 patients did not qualify for the study. During the study period, one patient was lost to follow-up and five patients died. A total of 119 patients completed 12 months of follow-up. Of those, 110 patients were maintained on TAC OD throughout the study; whereas nine were withdrawn from the TAC XL formulation and reconverted to TAC BID because of adverse events. Table 1 shows baseline characteristics of the study population. Patients had a median age of 53 years (range: 19–74 years). The time period between LT and enrollment in the study group ranged between 6.1 and 251 months.

TAC trough levels and dose requirements

At study entry, the mean TAC trough level concentration was 6.1 ± 2.3 ng/ml (Table 2), followed by a significant decline to 5.5 ± 2.1 ng/ml ($P = 0.016$) and 5.5 ± 2.2 ng/ml ($P = 0.019$) after 1 and 2 weeks, respectively. At week 1, TAC concentrations were lower in 62.4% of patients and higher in 36.0% of patients, compared with baseline. In 28.8% and 24.0% of patients, TAC concentrations were >25% lower and >25% higher than preconversion, respectively.

Compared with the start of the study, TAC doses were significantly higher at week 2 ($P = 0.003$), month 1 ($P = 0.003$), and month 3 ($P = 0.01$), respectively resulting in a significant TAC level increase at month 1 when compared with week 2 ($P = 0.014$) and stable TAC levels during further follow-up. The highest proportion (nearly one-third) of patients with TAC dose increases was observed at week 2; in 15 patients (12.1%), the TAC dose was increased >25% (>25–50% in 10 patients, >50–75% in none, >75–100% in three patients and >100% in two patients).

At months 6 and 9, the dose was decreased in nearly one-third of patients. Consequently, the mean TAC concentration at month 12 tended to be lower than TAC levels on previous visits (Table 2).

Graft function and graft rejection at month 12

There were no significant changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin at 12 months postconversion. No rejection episodes occurred during the course of the study.

Patient and graft survival

The Kaplan–Meier 12-month-estimated patient and allograft survival rates were both 96%. Three patients died during follow-up because of sepsis 233, 327, and 328 days postconversion and one patient died because of a recurrent neuroendocrine tumor after 23 days. One patient with fibrosing cholestatic hepatitis C experienced graft failure during the study, was relisted, and died on the waiting list 79 days after study entry.

Table 1. Patients' baseline characteristics.

Variable	Patients (n = 125)
Age (years)	51 ± 13.9
Male gender (%)	79 (63.2)
Primary indication for LT (%)	
HCV	23 (18.4)
ALD	19 (15.2)
AIH, PBC, PSC	16 (12.8)
HCC	12 (9.6)
HBV/HBV + HDV	11 (8.8)
Cryptogenic	11 (8.8)
Acute liver failure	12 (9.6)
Wilson's disease	5 (4.0)
Others	16 (12.8)
Time LT-enrollment (months)	77.4 ± 59.6
<1 year, 1–5 years, 6–10 years, >11 years after LT (%)	2 (1.6), 62 (49.6), 37 (29.6), 24 (19.2)
Arterial hypertension (%)	75 (60.0)
Antihypertensive medication (%)	68 (54.4)
No. antihypertensive drugs: n = 1, 2–3, 4–5 (%)	28 (22.4), 38 (30.4), 2 (1.6)
Hypercholesterolemia/ hypertriglyceridemia (%)	33 (26.4)/26 (20.8)
Lipid lowering agents (statins and/or fibrates) (%)	9 (7.2)
Diabetes (%)	39 (31.2)
Oral medication and/or insulin	27 (21.6)
TAC-based immunosuppression (%)	
Plus mycophenolate mofetil	39 (31.2)
Plus steroids	25 (20.0)
Plus sirolimus	8 (6.4)
TAC monotherapy/TAC-based double/triple immunosuppression (%)	70 (56.0)/36 (28.8)/ 19 (15.2)

Values are expressed as mean ± SD or percentages.
LT, liver transplantation; HCV, hepatitis C virus; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HDV, hepatitis D virus; BMI, body mass index; TAC, tacrolimus.

Table 2. Once-daily tacrolimus (TAC OD) doses, dose adjustments from previous visit over time and TAC OD predose concentrations.

	Baseline, *n* = 125	Week 1, *n* = 125	Week 2, *n* = 124	Month 1, *n* = 119	Month 3, *n* = 115	Month 6, *n* = 114	Month 9, *n* = 112	Month 12, *n* = 110
Dose*** (mg, mean ± SD)	4.1 ± 2.7	4.2 ± 2.7	4.4 ± 2.8*	4.5 ± 2.9*	4.5 ± 3.0**	4.4 ± 3.0	4.3 ± 2.9	4.2 ± 2.9
P-value versus previous visit	–	0.144	0.004	0.169	0.962	0.138	0.019	0.622
Dose increased (%)	–	33 (26.4)	38 (30.6)	31 (26.1)	26 (22.6)	23 (20.2)	13 (11.6)	20 (18.2)
TAC dose increase >25% (%)	–	11 (8.8)	15 (12.1)	11 (9.2)	12 (10.4)	9 (7.9)	6 (5.4)	6 (5.5)
Dose decreased (%)	–	12 (9.6)	18 (14.5)	22 (18.5)	21 (18.3)	33 (28.9)	33 (29.5)	25 (22.7)
TAC dose decrease >25% (%)	–	8 (6.4)	4 (3.2)	9 (7.6)	6 (5.2)	4 (3.5)	11 (9.8)	6 (5.5)
No change (%)	–	80 (64.0)	68 (54.8)	66 (55.4)	68 (59.1)	58 (50.9)	66 (58.9)	65 (59.1)
Predose concentrations**** (ng/ml, mean ± SD)	6.1 ± 2.3	5.5 ± 2.1**	5.5 ± 2.2**	5.9 ± 2.2	5.7 ± 2.1	5.9 ± 2.6	6.1 ± 2.6	5.6 ± 2.1
P-value versus previous visit	–	0.016	0.727	0.014	0.130	0.205	0.634	0.246

*$P < 0.005$ vs. baseline; **$P < 0.05$ vs. baseline.
***$P = 0.001$ for global comparison of doses at distinct timepoints according to Friedman test.
****$P = 0.011$ for global comparison of TAC levels at distinct timepoints according to Friedman test.

Renal function and cardiovascular risk factors

The evolution of renal function is shown in Table 3. The results indicate that serum creatinine values, urea, and cGFR remained stable throughout the 12 months post-conversion.

A total of 46 patients (36.8%) had no concomitant antihypertensive, antidiabetic and/or lipid lowering agents. Antihypertensive medication was administered in 54.4% and 62.5% of patients at baseline (Table 1) and at month 12, respectively. The mean number of antihypertensive drugs per patient diagnosed with arterial hypertension remained similar (1.67 ± 0.96 at baseline vs. 1.74 ± 1.00 after 12 months, $P = 0.634$) throughout the study. The doses of antihypertensive medication were decreased in three patients during follow-up. Three patients were diagnosed with borderline hypertension [9] at baseline and developed manifest arterial hypertension at month 12.

Fasting glucose levels (Table 3) and HbA1c values (6.27 ± 3.36%, 5.85 ± 1.04%, 6.32 ± 1.96%, and 6.07 ± 0.92% at baseline, months 1, 6, and 12, respectively) remained stable during 12 months of follow-up. Three and two patients were prescribed sulfonylureas (glimepiride) or glinides (repaglinide, nateglinide) at baseline and at month 12; two patients and one patient were treated with alpha-glucosidase inhibitors at baseline and at month 12, respectively. Insulin-dependent diabetes was apparent in 22 patients at baseline, compared with 24 patients at month 12 ($P = 0.248$). There was one case with *de novo* diabetes mellitus at month 12.

There was no significant difference in body mass index (BMI) before TAC conversion and at month 12 postconversion (mean BMI 26.3 ± 5.1 kg/m^2 vs. 26.4 ± 5.0 kg/m^2, $P = 0.534$). At study entry, hypercholesterolemia was apparent in 26.4% of patients, hypertriglyceridemia in 20.8% of patients and combined hyperlipidemia in 12.8% of patients. A statin was withdrawn in one patient and was newly prescribed in another patient during follow-up. Lipid values did not change significantly (Table 3) throughout the study.

Adverse events

The postconversion safety profile of TAC OD was unremarkable and was consistent with the known adverse events for patients treated with TAC BID. During the study period, most TAC OD-related adverse events (Table 4) reported were mild or moderate and short-lived. One patient experienced tumor recurrence, but no *de novo* malignancies were reported during the 12 months. Nine patients were reconverted to TAC BID because of side effects: Five patients were withdrawn

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